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PREPARATION OF TERT-BUTYLDIMETHYLSILYL (TBDMS) ENOL ETHERS USING POTASSIUM HYDRIDE IN THE PRESENCE OF TBDMS CHLORIDE

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Summary: TBDMS enol ethers can be readily prepared regio- and stereoselectively under equilibrating conditions in high yield by adding potassium hydride to a THF solution of ketone with TBDMS chloride in situ.

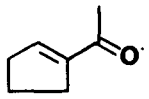
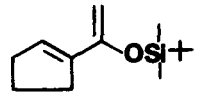
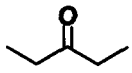
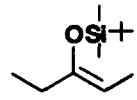
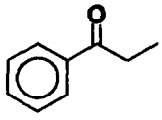
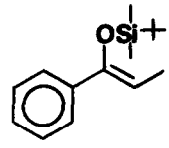
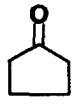
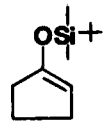
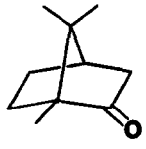
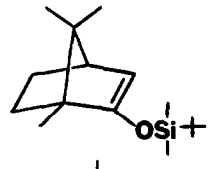
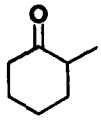
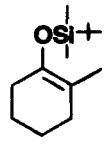
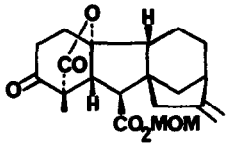
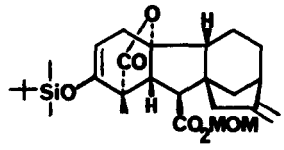
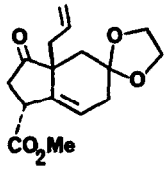
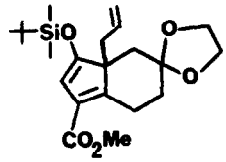
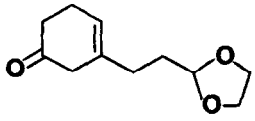
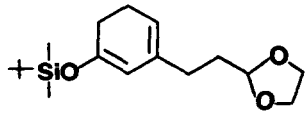
Recently we required a high yielding and straightforward procedure for the preparation of tert-butyldimethylsilyl (TBDMS) enol ethers. These "frozen enolates" can survive a variety of reaction conditions that would destroy their trimethylsilyl (TMS) counterparts (e.g. Birch reduction, methyl lithium) and yet they can react with electrophiles either directly, or with activation, for example, through treatment at -78° with fluoride ion in aprotic media.[1]

We needed in particular the diene (1b) (see Table) for use as a Diels-Alder substrate under conditions which had previously decomposed the sensitive TMS analogue. In early preparations, we used a standard amide base treatment for deprotonation of the precursor acetylcyclopentene (1a) (LDA) and trapped the lithium enolate through the subsequent addition of TBDMS chloride;[2] however, relatively poor yields of diene (1b) were obtained (26%) after work-up.

We considered, therefore, the prospect of minimizing side-reactions by trapping the generated enolate with TBDMS chloride in situ, and of using potassium hydride as the base since this is poorly nucleophilic towards electrophilic carbon and was not expected to react quickly with the TBDMS chloride.[3] It was envisaged that work-up could simply involve filtration through Florisil and concentration. In practice this proved to be the case and diene 1b was thus prepared (see General Procedure) in 98% isolated yield and 61% after distillation.[1]

In order to investigate the general applicability of this method we sought to prepare a range of TBDMS enol ethers from the structurally and functionally diverse ketones listed in the Table.[4] In each case the isolated yield was excellent and the products usually sufficiently pure for immediate use.[3]

TABLE

ENTRY	KETONE [a]	YIELD[4] SILYL ENOL ETHER (MAJOR : MINOR)	MAJOR ISOMER [b]
1		98% (61% after distillation; labile to silica)	
2		90% (95:5) +1eq HMPA (97:3)	
3		∿100%	
4		98%	
5		87% (after distillation; labile to silica)	
6		95% +6.9eq HMPA (98:2)	
7		88%	
8		∿100%	
9		90%	

We note that the thermodynamically more stable Z-isomer (2b)[5] is formed stereoselectively from 3-pentanone (2a) and that the addition of 1 eq hexamethylphosphoramide (HMPA) marginally improves the Z:*E* isomer ratio to 97:3. This indicates that equilibration between enolate and ketone is relatively faster than trapping with TBDMS chloride, and that HMPA enhances the rate of equilibration more than the rate of trapping. Support for this conclusion comes from the highly regioselective conversion of 2-methylcyclohexanone (6a) into the "thermodynamic" tetrasubstituted silyl enol ether (6b) when HMPA is included in the reaction mixture. In the absence of HMPA, the trisubstituted silyl enol ether is predominantly formed with (6b) in a 56:44 ratio.

It is notable that the high regioselectivity for the "thermodynamic" silyl enol ether (6b) is equivalent to that seen for making its TMS analogue from (6a) using bromomagnesium diisopropylamide and TMS chloride, which is the most regioselective method known for making "thermodynamic" TMS enol ethers.[6] Our method for making TBDMS enol ethers has, however, additional and important features: it also works well with ketones which are prone to self (aldol) condensation e.g. (1a) and (4a)[7] or to degradation e.g. (7a) and (8a) in the presence of base, or are difficult to enolize and derivatize e.g. (+)-camphor (5a).[8] Furthermore, the selectivity for "thermodynamic" TBDMS enol ethers is effectively complementary to that of a new procedure for making "kinetic" TMS enol ethers using lithium dialkylamides in the presence of TMS chloride.[9]

Thus, it appears that the present method is unique in its high regio- and stereoselectivity, simplicity, and mildness for making TBDMS enol ethers. These attributes are facilitating an on-going study of TBDMS enol ether reactivity towards electrophiles that will be reported in due course.

GENERAL PROCEDURE.

Potassium hydride (40 mmol) was added under a stream of nitrogen to a dry THF (40 ml) solution of ketone (10 mmol) and TBDMS chloride (13 mmol) at -78° (see Table for variants with HMPA). The stirred mixture was warmed slowly to 25° and the reaction monitored by tlc. When no ketone remained [<1.5 h; (5a) 18 h; (6a)+HMPA, 2 h with further 1.3 eq TBDMS chloride after 1 h] the reaction mixture was filtered through a column of Florisil (25 mm x 100 mm) into a dry base-washed flask, and concentrated to give the TBDMS enol ether.

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2. R.E. Ireland, W.J. Thompson, N.S. Mandel, and G.S. Mandel, J. Org. Chem., 44, 3583 (1979).

3. The less substituted TMS chloride, however, is a known potassium hydride "poison": C.A. Brown, J. Org. Chem., 39, 3913 (1974). If HMPA is included in the reaction mixture, silane by-product is also formed.

4. Yields reported are for isolated, chromatographically homogeneous products. Silyl enol ether (8b) was prepared by Dr A.D. Stuart and (9b) by Dr R.D. Dawe. Isomer ratios were determined by GLC and/or ^{1}H NMR and comparison with authentic samples. New compounds gave satisfactory elemental analyses (combustion or HRMS) and had consistent spectroscopic characteristics; selected data are: (2b) b.p. 55°/0.5 mm (Kugelrohr); ^{1}H NMR ($CDCl_3$) δ 0.12 (s, 6H), 0.94 (s, 9H), 1.03 (t, J=7.5Hz, 3H, partly obscured by t-Bu peak, CH_3), 1.53 (d, J=7Hz, 3H, broadened by homoallylic coupling >1Hz, =C-CH_3), 2.04 (q, J=7.5Hz, 2H, broadened by allylic and homoallylic coupling >1 Hz, CH_2), 4.50 (q, J=7Hz, 1H, broadened by allylic coupling >1 Hz, =C-H). (3b) b.p. 90°/0.2 mm; ^{1}H NMR (CCl_4) δ 0.00 (s, 6H), 1.07 (s, 9H), 1.81 (d, J=7Hz, 3H, CH_3), 5.20 (q, J=7Hz, 1H, =C-H), 7.19-7.48 (m, 5H, ArH). (4b) b.p. 100°/2.2 mm; ^{1}H NMR ($CDCl_3$) δ 0.13 (s, 6H), 0.91 (s, 9H), 1.83 (m, 2H, -CH_2-), 2.23 (m, 4H, =C-CH_2), 4.68 (brs, $W_{\frac{1}{2}}$ = 3Hz, 1H, =C-H). (5b) b.p. 105°/2.0 mm; ^{1}H NMR ($CDCl_3$) δ 0.11 (s, 3H), 0.15 (s, 3H), 0.72 (s, 3H), 0.88 (s, 6H), 0.93 (s, 9H), 2.17 (t, J=3.4Hz, 1H, -CH-), 4.56 (d, J=3.4Hz, 1H, =C-H). (6b) b.p. ~80°/0.8 mm; ^{1}H NMR ($CDCl_3$) δ 0.10 (s, 6H), 0.92 (s, 9H), 1.57 (brs, $W_{\frac{1}{2}}$ = 4Hz, 3H, CH_3), 1.59 (m, 4H, overlapping with 1.57 signal, -CH_2-), 1.98 (m, 4H, =C-CH_2). (7b) ^{1}H NMR (CCl_4) δ 0.11 (s, 6H), 0.87 (s, 9H), 1.08 (s, 3H, CH_3), 3.38 (s, 3H, OCH_3), 4.66 (brd, J=3Hz, 1H, H-2), 4.76 and 4.88 (2 brs, $W_{\frac{1}{2}}$ = 5Hz, 2H, =CH_2). (8b) ^{1}H NMR ($CDCl_3$) δ 0.22 (s, 6H), 0.95 (s, 9H), 3.78 (s, 3H, CO_2CH_3), 3.98 (m, 4H, CH_2O), 4.87 (m, 2H, =CH_2), 5.00 (brs, $W_{\frac{1}{2}}$ = 6Hz, 1H, OC=C-H), 5.29 (m, 1H, =C-H). (9b) ^{1}H NMR ($CDCl_3$) δ 0.17 (s, 6H), 0.91 (s, 9H), 1.75 (m, 2H, -CH_2-), 2.13 (m, 6H, =C-CH_2), 3.91 (m, 4H, CH_2O), 4.86 (t, J=6Hz, 1H, OCHO), 5.03 (brs, $W_{\frac{1}{2}}$ = 4Hz, 1H, OC=CH), 5.16 (brs, $W_{\frac{1}{2}}$ = 11Hz, 1H, =CH).

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